

EXPRESSION OF ENZYMES THAT METABOLIZE MEDICATIONS

V.E. Wotring^{1,2} and C.P. Peters³

¹JSC Pharmacology (SK3), 2101 NASA Rd 1, Houston, TX 77058; Universities Space Research Association;

³Bethel University, Department of Chemistry, 3900 Bethel Drive, St Paul, MN 55112

INTRODUCTION

Increased exposure to radiation is one physiological stressor associated with spaceflight and it is feasible to conduct ground experiments using known radiation exposures. The health of the liver, especially the activity rate of its metabolic enzymes, determines the concentration of circulating drugs as well as the duration of their efficacy. While radiation is known to alter normal physiological function, how radiation affects liver metabolism of administered medications is unclear. Crew health could be affected if the actions of medications used in spaceflight deviated from expectations formed during terrestrial medication use. This study is an effort to identify liver metabolic enzymes whose expression is altered by spaceflight or by radiation exposures that mimic features of the spaceflight environment.

METHODS

Using procedures approved by the Animal Care and Use Committee, mice were exposed to either ¹³⁷Cs (controls, 50 mGy, 6Gy, or 50 mGy + 6Gy separated by 24 hours) or 13 days of spaceflight on STS 135. Animals were anesthetized and sacrificed at several time points (4 hours, 24 hours or 7 days) after their last radiation exposure, or within 6 hours of return to Earth for the STS 135 animals. Livers were removed immediately and flash-frozen in liquid nitrogen. Tissue was homogenized, RNA extracted, purified and quality-tested. Complementary DNA was prepared from high-quality RNA samples, and used in RT-qPCR experiments to determine relative expression of a wide variety of genes involved in general metabolism and drug metabolism.

RESULTS

Results of the ground radiation exposure experiments indicated ~65 genes of the 190 tested were significantly affected by at least one of the radiation doses. Many of the affected genes are involved in the metabolism of drugs with hydrophobic or steroid-like structures, maintenance of redox homeostasis and repair of DNA damage. Most affected genes returned to near control expression levels by 7 days post-treatment. Not all recovered completely by the final time point tested: with 6 Gy exposure, metallothionein expression was 132-fold more than control at the 4 hr time point, and fell at each later time point (11-fold at 24 hrs, and 8-fold at 7 days). In contrast, there were other genes whose expression was altered and remained relatively constant through the 7 day period we tested. One example is Cyp17a1, which showed a 4-fold elevation at 4 hrs after exposure and remained constant for 7 days after the last treatment. Spaceflight samples evaluated with similar methods and comparisons will be made between the radiation-treated groups and the spaceflight samples.

CONCLUSION

It seems likely that radiation exposure triggers homeostatic mechanisms, which could include alterations of gene expression. Better understanding of these pathways could aid in optimizing medications doses given to crewmembers who require treatment and eventually, to development of new countermeasures to ameliorate or prevent radiation-induced damage to cells and tissues.